J MATER SCI **41** (2006) 2393–2404

Investigation of the influence of freeze-thaw processing on the properties of polyvinyl alcohol/polyacrylic acid complexes

M. J. D. NUGENT, C. L. HIGGINBOTHAM*
Centre for Biopolymer and Biomolecular Research, Athlone Institute of Technology, Dublin Rd, Athlone, Co. Westmeath, Ireland
E-mail: mnugent@ait.ie
E-mail: chigginbotham@ait.ie

Physically crosslinked poly (vinyl alcohol)/poly (acrylic acid) hydrogels were prepared by freeze thaw processing. The hydrogels were formed in, either, water or a water/DMSO mixture and the chemical, mechanical, and thermal properties were determined by FTIR analysis, rotational rheometry and modulated DSC respectively. The results indicate that the hydrogels containing DMSO are significantly stronger than those containing water alone at temperatures between 20 and 40°C. Materials with different characteristics can be created by varying the solvent and the polymer feed ratios. DSC analysis indicated that thermal transitions are present at temperatures that may make these hydrogels useful in temperature sensitive drug delivery systems. © *2006 Springer Science + Business Media, Inc.*

1. Introduction

In recent times, there has been considerable effort and focus in creating a stimuli responsive material that is biocompatible. This would make targeted delivery of drugs possible. Coatings using these materials would increase versatility in invasive medical devices. The main thrust of the research and development, in this area, has been focussed on hydrogels.

The term hydrogel is used to describe materials that are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids [1–4]. Hydrogels have important applications in the areas of controlled drug delivery, as coatings in gastrointestinal pharmaceutical applications and as dissolution and binding agents in tablets [5–7].

Hydrogels can be prepared that react to changes in the environment. Properties such as volume, conductivity or viscosity may change in response to pH, temperature, ionic strength and mechanical stress. Hydrogels may be composed of homopolymers, copolymers or blends and are insoluble due to the presence of chemical cross links (covalent bonding) or physical cross links, such as entanglements or crystallites [8–10].

One method of creating a hydrogel without utilization of chemical cross links is the production of poly (vinyl alcohol) (PVA) hydrogels by freeze/thaw processing [11–13]. PVA hydrogels prepared using freeze/thaw cycling have great potential for biomedical and drug delivery applications due to desirable mechanical and swelling properties [14–16]. These hydrogels are prepared by exposing aqueous PVA solutions to repeated cycles of freezing and thawing, which results in the formation of crystallites which render the material insoluble in water. The strength, stability and swelling ratio of the gels are a function of the solution concentration, freezing time and the number of freeze/thaw cycles. In order to improve the functionality of the hydrogels, PVA is often combined with poly (acrylic acid) (PAA) [17–19].

When a DMSO/water solution of PVA is frozen, a transparent gel with high elasticity is created [20–24]. The properties are dependent on the ratio of water to DMSO solvent. The gelation rate is as a function of polymer concentration, quenching temperature and degree of polymerization [25]. The effects of DMSO on a blend of PVA/PAA solutions, which are frozen, are not yet fully characterized.

The use of hydrogels in biomedical applications requires a detailed knowledge of the physical properties. The characterisation of gels is complex as there are in essence two components involved, a solid phase and a

---

*Author to whom all correspondence should be addressed.

0022-2461 © *2006 Springer Science + Business Media, Inc.*
DOI: 10.1007/s10853-006-7075-9

liquid phase. A gel can be characterized by a storage modulus G′ which exhibits a pronounced plateau extending to times at least of the order of seconds and by a loss modulus G′′ which is considerably smaller than the storage modulus in the plateau region [26]. Oscillatory shear rheometry, differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FTIR) can be used to characterise polymer hydrogels which are used in biomedical applications, such as long term degrading hydrogels, bioadhesive gels and drug delivery systems [27–32].

In the present study PVA/PAA blends were prepared, and their properties examined, in order to determine the effect of different polymer feed ratios and different solvent ratios on the mechanical and physical properties.

The novel aspect of the present research is the differing functionality created by varying the solvents and by changing the polymer feed ratios. Important properties for hydrogels are mechanical properties and thermal properties. Different thermal transitions mean that, for example, drug release could be achieved at different rates for different temperatures. Greater mechanical strength could have an impact on the use of the materials in the body. By studying these properties, it is possible to gain greater insight into the complex interactions of the polymers and the different solvents.

2. Materials and methods

2.1. Preparation of samples

PVA (weight average molecular weight 146,000–186,000) and PAA (weight average molecular weight 3,000,000) used in this study were supplied by Aldrich. Solutions were prepared by mixing polymer powder (1 g) with distilled water (50 mls) using the polymer feed percentages shown in Table I. The samples were prepared using either (i) 100% water or (ii) 10 wt% aqueous solution of dimethyl sulphoxide (DMSO).

Dissolution was achieved by heating the mixture to 80°C for 90 min, while slowly stirring. When the polymer was no longer apparent and the mixture was clear, the solution was cooled to 70°C. To remove any bubbles the solution was placed in an ultra sonic water bath at 70°C for five minutes. The solution was placed in an oven at 70°C to further aid in the removal of bubbles. A small portion of the liquid was cast in a silicone mould (W.P. Notcutt, Middlesex) and allowed to dry at room temperature. This process is referred to as solvent casting (SC). The SC samples were used for DSC scans and FTIR analysis. The remaining solution was removed from the oven and placed in a polystyrene beaker. The beaker was placed in a trough and approximately 500 mls of liquid nitrogen was added over a period of ten minutes. The solidified solution was allowed to stand for 24 h, removed and placed in a petri dish. Upon thawing a gel was formed. This process is referred to as freeze/thawing (F/T). The F/T samples were characterised by DSC, FTIR analysis and rheometry. This analysis was performed on a given sample within a few days to minimise the effect of aging. Fig. 1 shows a picture of a typical gel formed by this method.

TABLE I Polymer feed ratios used in the preparation of the hydrogel complexes

PAA%	0	10	20	30	40	100
PVA %	100	90	80	70	60	0

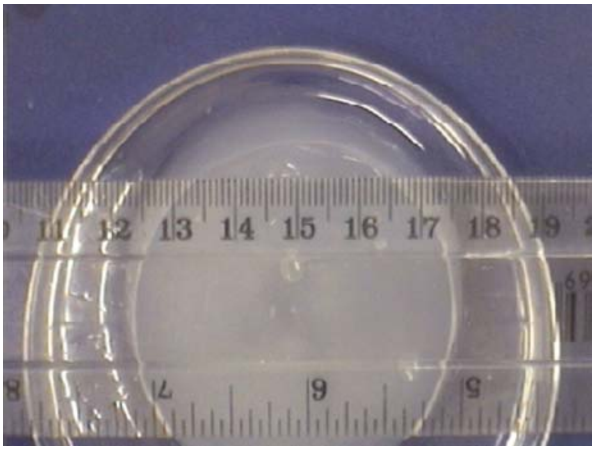

Figure 1 A picture of a typical gel formed by the freeze thaw process.

2.2. Modulated differential scanning calorimetry

Modulated differential scanning calorimetry (MDSC) was carried out using a TA instruments calorimeter. A sample of between 10 and 12 mg was weighed out and the tests were carried out in sealed aluminium pans. The samples were cooled to −20°C, the modulation was +/− 1.00°C every 60 sec and the temperature was ramped from −20° to 260.00°C.

2.3. Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy was carried out on samples that had being exposed to atmospheric conditions for a minimum of 7 days using a Nicolet Avator 360 FTIR, with a 32 scan per sample cycle.

2.4. Rheometry

Rheological measurements were performed on a strain-controlled TA instrument AR1000. The geometry used was a 4 cm diameter parallel steel plate. The temperature was ramped from 20° to 80°C with tests carried out at a two degree interval. The tests were in an oscillation form with a strain sweep of 1 Hz, 5.5 Hz, and 10 Hz with a constant strain, γ, of 10%. In all experiments, a weak normal force was applied to the surface of the sample discs in order to avoid the sweeping of the gel from the tool plates. This force resulted in a slight compression of the sample. All rheometry was carried out with disc shaped samples of the hydrogels of diameter 40 mm

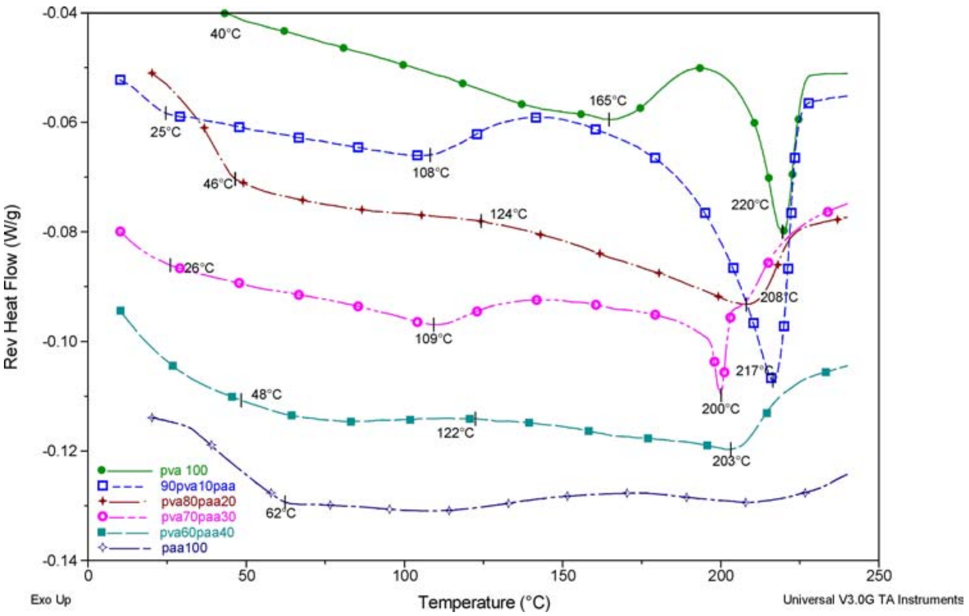

Figure 2 Reversible thermal transitions in 100% aqueous samples (F/T) *F/T = 1 freeze/thaw cycle, *SC = solvent cast.

and average thickness of 12 mm. Each measurement was performed, at least twice, on two different disc specimens from the same sample.

3. Results and discussion

3.1. Appearance of gels

The samples which were composed of 100% PVA did not form gels. It was noted that the strength, stability and swelling ratio of gels were a function of the solution concentration, freezing time and number of freeze/thaw cycles [13]. The addition of PAA resulted in the formation of a hydrogel due to the fact that the high molecular weight of the PAA effectively increased the concentration of polymer in the sample. In addition to this the intermolecular interaction between PVA and PAA, likely due to hydrogen bonding was promoted to yield small crystalline nuclei [13]. The samples produced using pure water and the various polymer feed ratios were less opaque than the samples containing DMSO and water. The opaque nature of the samples containing DMSO was due to phase separation and increased crystallinity of the material [33–35]. Samples which were solvent cast before the freezing process showed marked differences in physical appearance between the DMSO samples and the aqueous samples. The samples cast from water tended to dry and shrink, reducing in diameter by up to 30 percent. The samples which originally contained DMSO retained the shape of the mould in which they were cast.

3.2. Modulated differential scanning calorimetry

MDSC was used instead of conventional DSC, due to the complex interaction of the polymers and solvents. MDSC is more effective at determining the transitions from the different components of a blend [36]. In MDSC the total heat flow and the two individual components can be distinguished as the heat capacity component or reversing heat flow and the kinetic component or non-reversing heat flow. The use of reversible heat flow shows the underlying transitions and reduces the masking effect of solvents. Park *et al.* found that PVA exhibits peaks at 85°C and 143°C, and a large peak above 210°C. The peak at 85°C, designated as the α relaxation, represents the glass transition temperature of PVA. The relaxation observed at 143°C, designated as the β relaxation, is due to the relaxation in the PVA crystalline domains. The third relaxation, which occurs at a temperature between 200°C and 260°C, is caused by the melting of the crystalline domains of PVA [37]. PAA has a Tg of 106°C [38].

DSC graphs of 100% PVA polymer produced in water and hydrogels containing 10%, 20%, 30%, 40% and 100 % PAA are presented in Fig. 2 (F/T samples) and Fig. 3 (SC samples).

The Tg of the 100% PVA samples was at 40°C for both F/T and SC. These low values may be due to the presence of water in the samples from the F/T and the SC process. This may have had a plasticizing effect which effectively reduces the Tg. Watase and Nishinari have shown that gels with a high concentration of PVA show rubber elastic behaviour up to 45°C and after this point a transition to liquid-like behaviour occurs [21]. This transition would appear to be present in the samples prepared using 100% aqueous solutions. The Tg of 100% PAA has been reduced by the effect of the water and occurs at 62°C.

The α relaxation occurs between 25°C and 48°C for both the F/T and SC samples. The major difference is that the peaks appear more distinct with the SC samples. The F/T process may make the hydrogels more homogenous

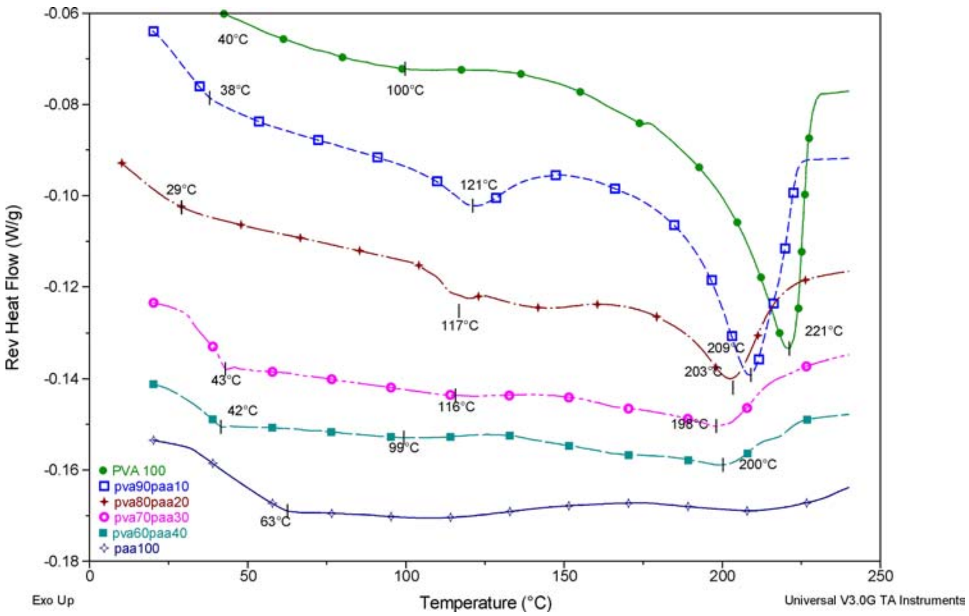

Figure 3 Reversible Thermal transitions in 100% aqueous samples (SC). *F/T = 1 freeze/thaw cycle. *SC = solvent cast.

with an increasing broadening of the endothermic peak. Willcox *et al*. state that an endotherm present at 90°C is indicative of secondary micro crystallite formation [12]. For both F/T and SC samples transitions occur between 99°C and 122°C which may be due to secondary micro crystallite formation.

PVA exhibited a relatively large and sharp endothermic curve, with a peak at around 220°C, while PAA, which is amorphous, had no endothermic curve. This is similar for both the SC and the F/T samples. As the content of PAA increased, the endothermic curve of PVA became broader and its peak shifted to a lower temperature. By blending PVA with an increasing amount of PAA, the endothermic peak of PVA became less prominent and disappeared for 100 wt% PAA. The depression of the melting temperature and the peak broadening indicate that the ordered association of the PVA molecules was decreased by the presence of PAA. The melting temperature depression is caused by morphological changes and the differing chemical groups. The morphological changes involve the thickness of the crystallites and the degree of crystallinity [37].

If the SC samples and the F/T samples are contrasted, it can be clearly seen that the peaks in the crystalline melting region, for the F/T samples are sharper, implying more ordered structure. The F/T process has produced more crystallinity. This difference is more apparent because of MDSC; conventional DSC would not have highlighted this aspect.

MDSC graphs of 100% PVA polymer produced in 10 wt% DMSO and hydrogels containing 10, 20, 30, 40 and 100% PAA are presented in Fig. 4 (F/T samples) and Fig. 5 (SC samples).

DMSO is a polar solvent with a large dielectric constant and its affinity for water is very high. For DMSO/water PVA gels, Tanigami *et al*. found that the thermal transitions below 100°C, for one day old gels, were difficult to determine as the endotherms were not obvious [39]. This is indeed the case for the F/T samples, where it is difficult to observe any transitions below 100°C, with the exception of 70% PVA and 30% PAA, which has a transition of 43°C. It is also difficult to determine transitions for 100% PAA for both F/T and SC.

The lack of transitions for the F/T gels, suggest that the chains are highly constrained by the entanglement of the two polymers and by the action of the solvent. For the SC gels it is possible to observe transitions under 100°C and this would suggest less constraint.

These transitions range from 48 to 81°C for the SC blends. The reason for this constraint of chain movement is suggested by the comparison of the melting points of the SC 10 wt% DMSO blends with the F/T 10 wt% DMSO blends. The SC samples have a sharp melting endotherm in the region of 183 to 224°C, this melting endotherm is reduced and barely visible for the F/T samples. The F/T process may have resulted in a different micro crystalline structure, which was suggested by Wilcox [12]. Alternatively the F/T process has resulted in phase separation and increased interaction with the solvent.

PVA gels are believed to consist of crystalline regions consisting of junction zones and amorphous regions consisting of long flexible chains [20]. Physical junctions in polymer gels may be classified into at least four types: crystallites for crystalline polymers, double helical structure for biological polymers, nodules for block copolymers and polymer -solvent complexes [25]. If a homogeneous high-temperature mixture of two components is rapidly cooled to a lower temperature, then a sudden phase

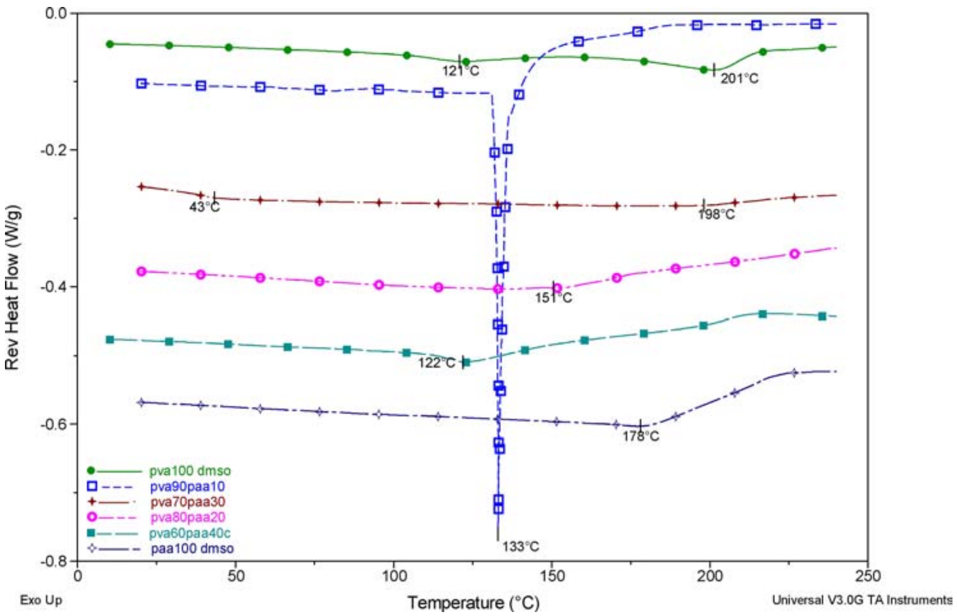

Figure 4 Thermal transitions in 10 wt% DMSO samples (F/T). *F/T = 1 freeze/thaw cycle. *SC = solvent cast

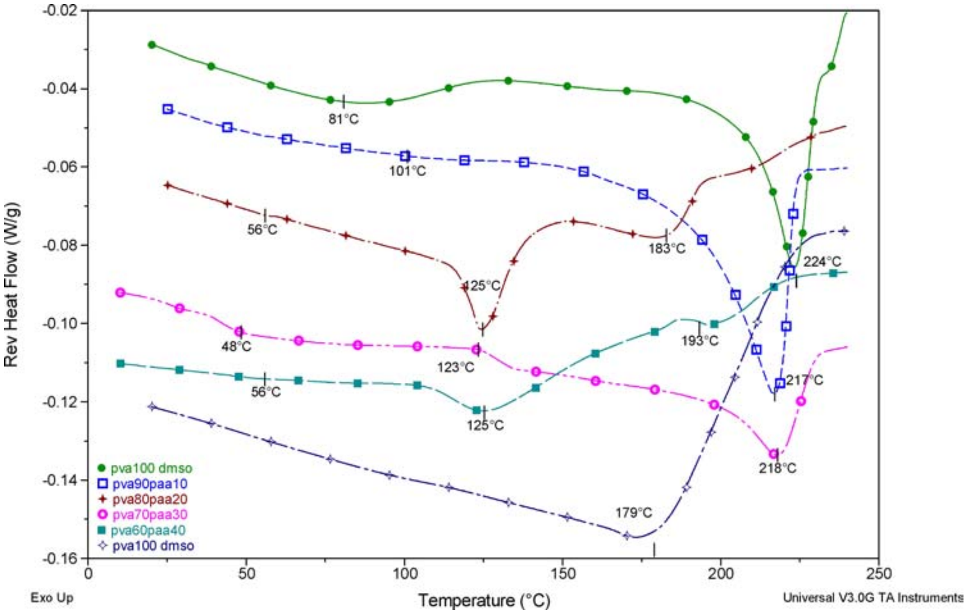

Figure 5 Reversible Thermal transitions in 10 wt% DMSO samples (SC). *F/T = 1 freeze/thaw cycle. *SC = solvent cast.

separation can set in. That is, the mixture becomes inhomogeneous and forms a fine-grained structure, more or less alternating between the components. This is known as spinodal decomposition and occurs in gel formation containing PVA and DMSO [25].

The gels containing PAA, PVA and DMSO, would appear from the results to have formed a gel by phase separation as there are no distinct crystalline melting endotherms, with the exception of the 90% PVA and 10% PAA. This peak is at 133°C, which is lower than the melting point of the aqueous hydrogels and would suggest a different crystalline structure or a multi phase structure, such as coexistent polymer-rich and polymer-poor phases [39].

The thermal transitions are indistinct which could indicate that micro-scale phase separation may have taken place, as opposed to distinct peaks which would indicate separate regions. The appearance of the gels is opaque which would be the case if phase separation had occurred [40].

3.3. Fourier transform infrared spectroscopy

Peppas *et al*. discusses drug diffusion in an IPN of PAA hydrogels and states that absorption peak is present at 3370 cm^{-1} due to the presence of an-OH group [41]. Hassan *et al*. in the discussion of PVA gels refer to

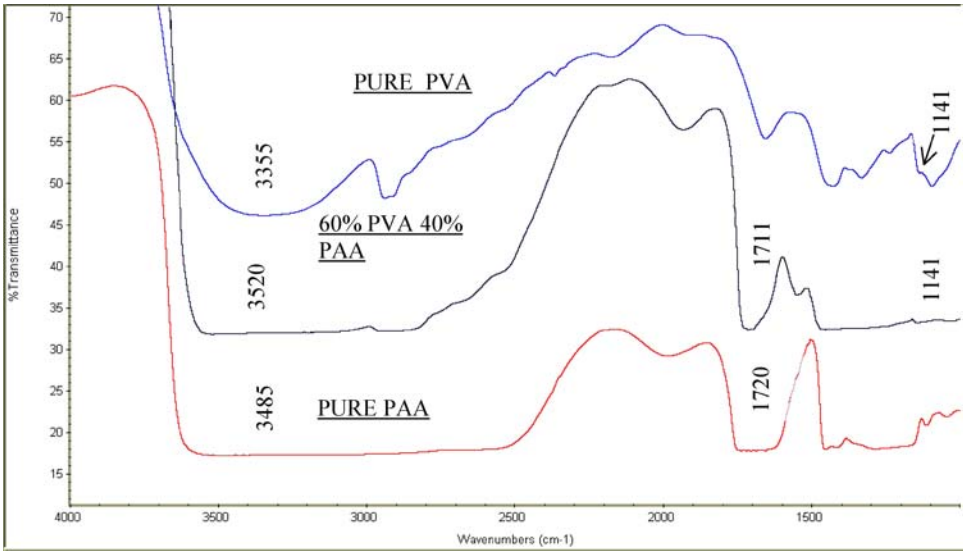

Figure 6 FTIR spectrum of pure PVA, a blend of 60%PVA/40%PAA and pure PAA for 100% aqueous samples.

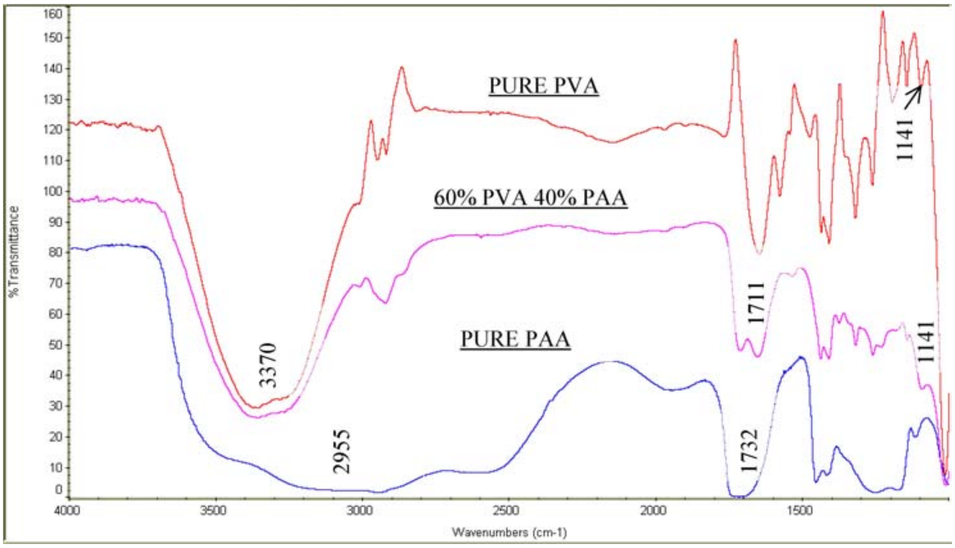

Figure 7 FTIR spectrum of pure PVA, a blend of 60%PVA/40%PAA and pure PAA for 10% DMSO samples.

an absorption peak at 1141 cm^{-1}, which is indicative of PVA crystallinity, this arises from a C-C stretching mode and increase with an increase in the degree of crystallinity [13]. Young *et al*. state that the stretching vibration of hydroxyl groups in PVA occurs at 3445 cm^{-1} and stretching vibration of carbonyl groups of the PAA occurs in the region of 1720 cm^{-1} [15]. Fig. 6 shows the FTIR spectrum of pure PVA, a blend of 60%PVA/40%PAA and pure PAA for 100% aqueous samples. Fig. 7 shows the FTIR spectrum of pure PVA a blend of 60%PVA/40% PAA and pure PAA for 10 wt % DMSO. Stretching vibration spectrum of carboxyl groups of PAA appears at 1732 cm^{-1} and this shifts to 1711 cm^{-1}, with reduced intensity indicating the presence of intermolecular hydrogen bonding between −COOH of PAA and-OH of PVA. This effect is more apparent in the presence of DMSO and increases with higher concentrations of PAA. A peak at 1141 cm^{-1} is present in the hydrogels, indicating that a crystalline effect is occurring.

3.4. Rheometry

Data reported in the literature on the mechanical properties of hydrogels are mostly obtained in tension/compression or using dynamic mechanical analysis. Dynamic mechanical methods have been successfully used to characterize the thermo/rheological properties of gel systems for polymeric films, for solid dosage coatings and as wound dressings [31]. To examine the stress strain relationship for the hydrogels, they were subjected to an alternating strain, while simultaneously measuring the stress. For viscoelastic behaviour, when equilibrium is reached, the stress and strain will both vary sinusoidally, but the strain lags behind the stress. These relationships are shown

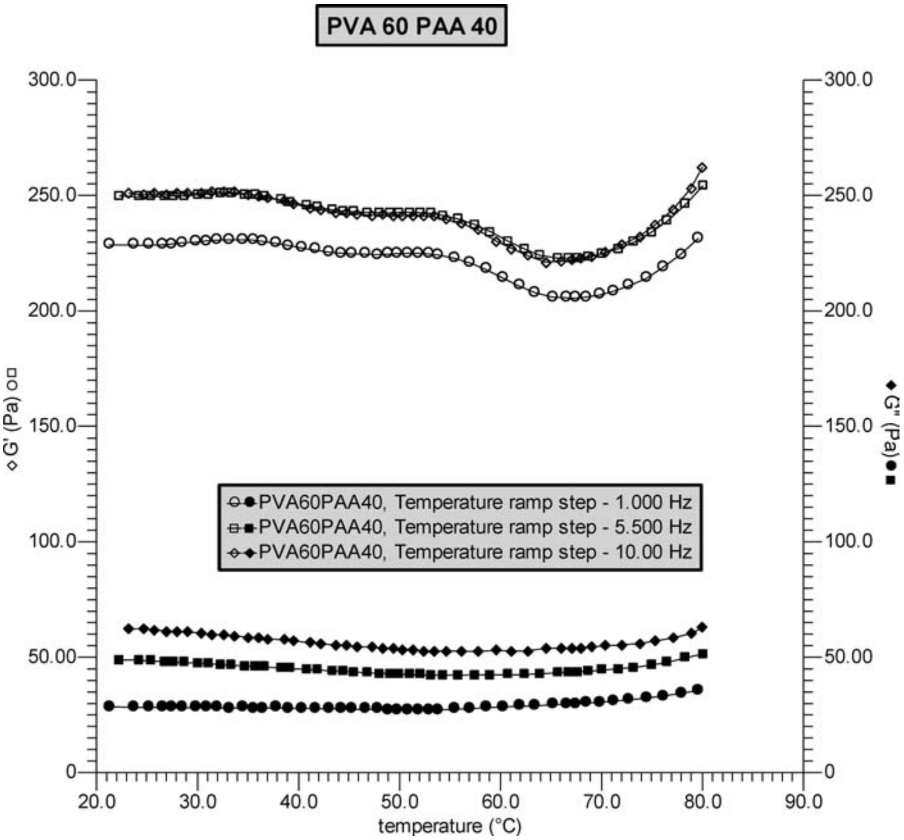

Figure 8 Rheological results for 60 wt% PVA 40 wt% PAA, aqueous hydrogels.

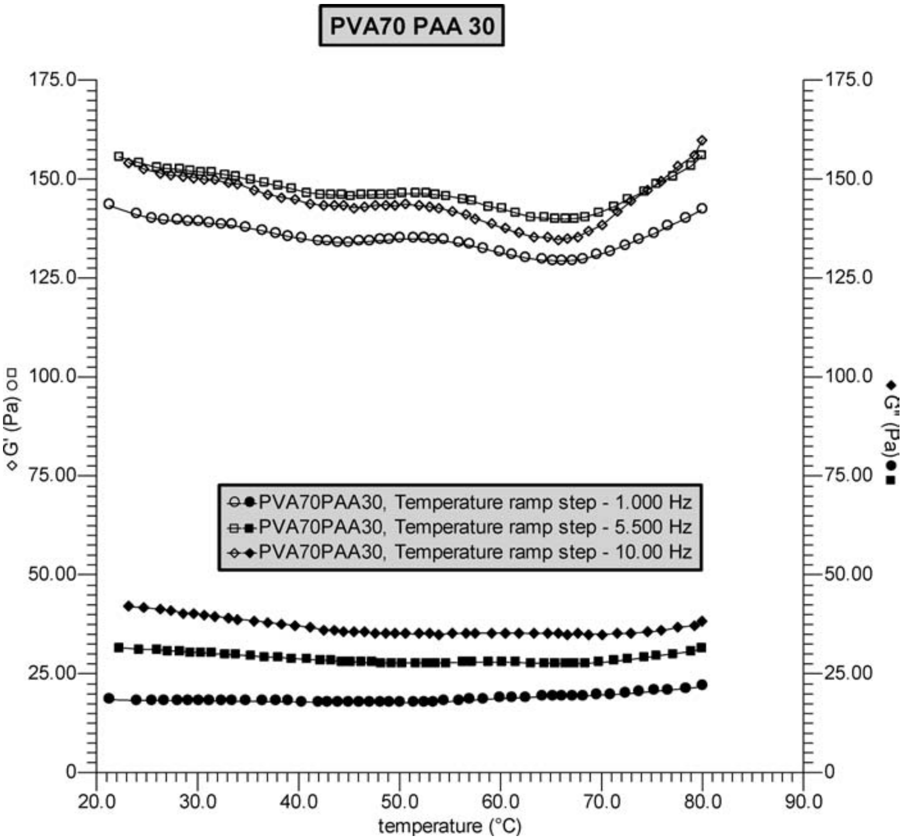

Figure 9 Rheological results for 70 wt% PVA 30 wt%, aqueous hydrogels.

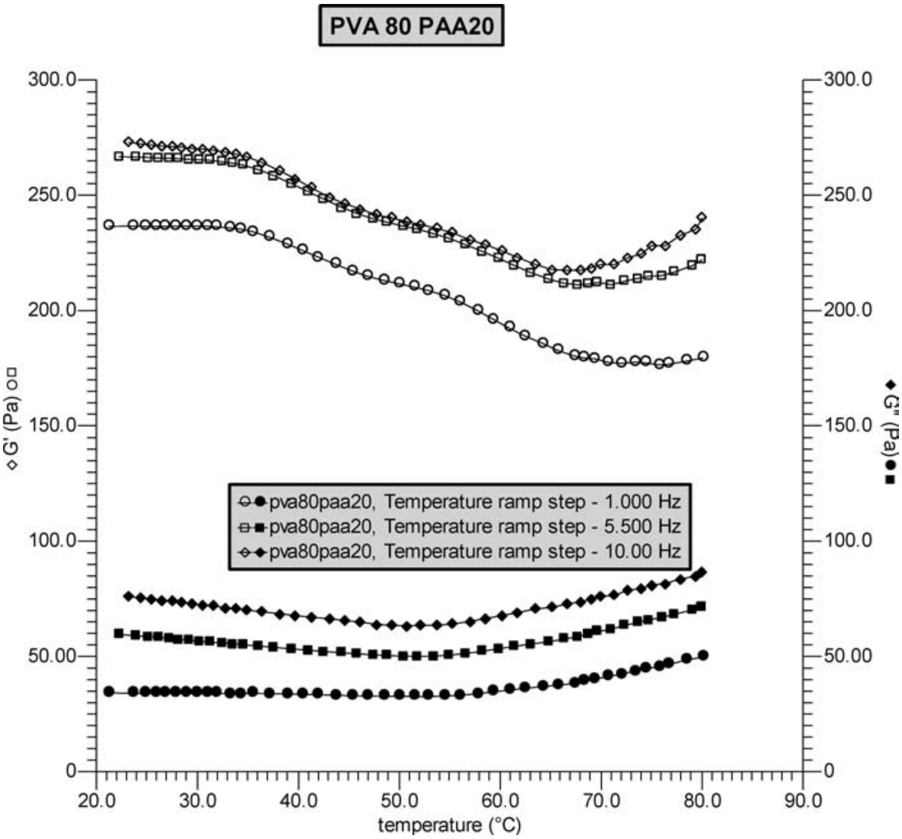

Figure 10 Rheological results for 80 wt% PVA 20 wt% PAA, aqueous hydrogels.

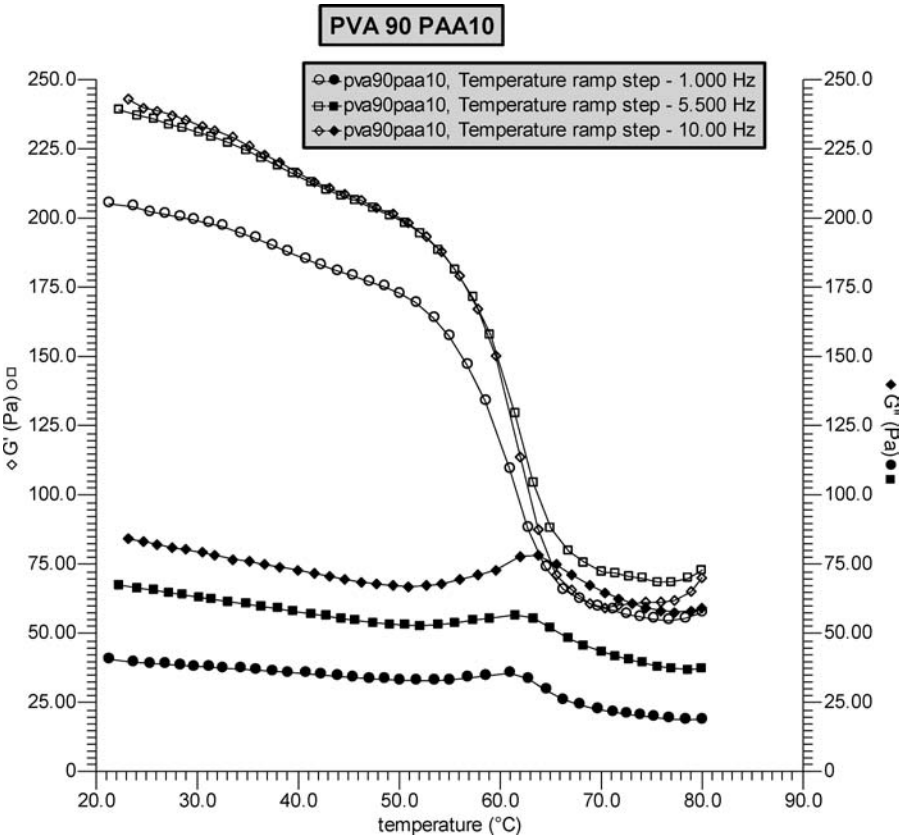

Figure 11 Rheological results for 90 wt% PVA 10 wt% PAA, aqueous hydrogels.

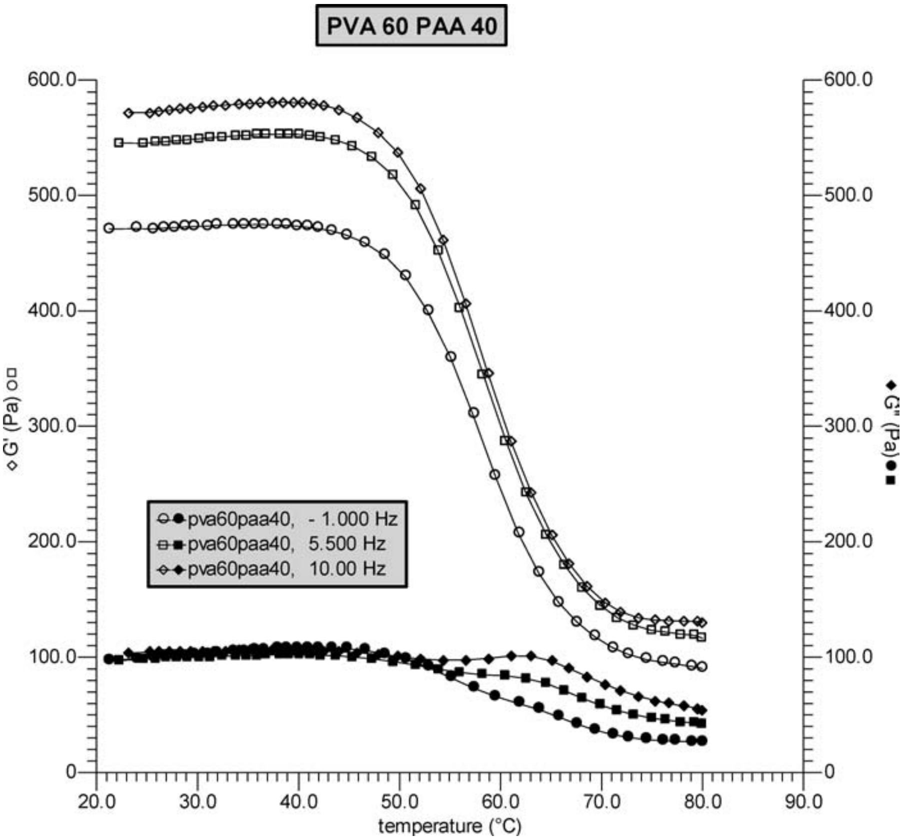

Figure 12 Rheological results for 60 wt% PVA 40 wt% PAA, 10 wt% DMSO hydrogels.

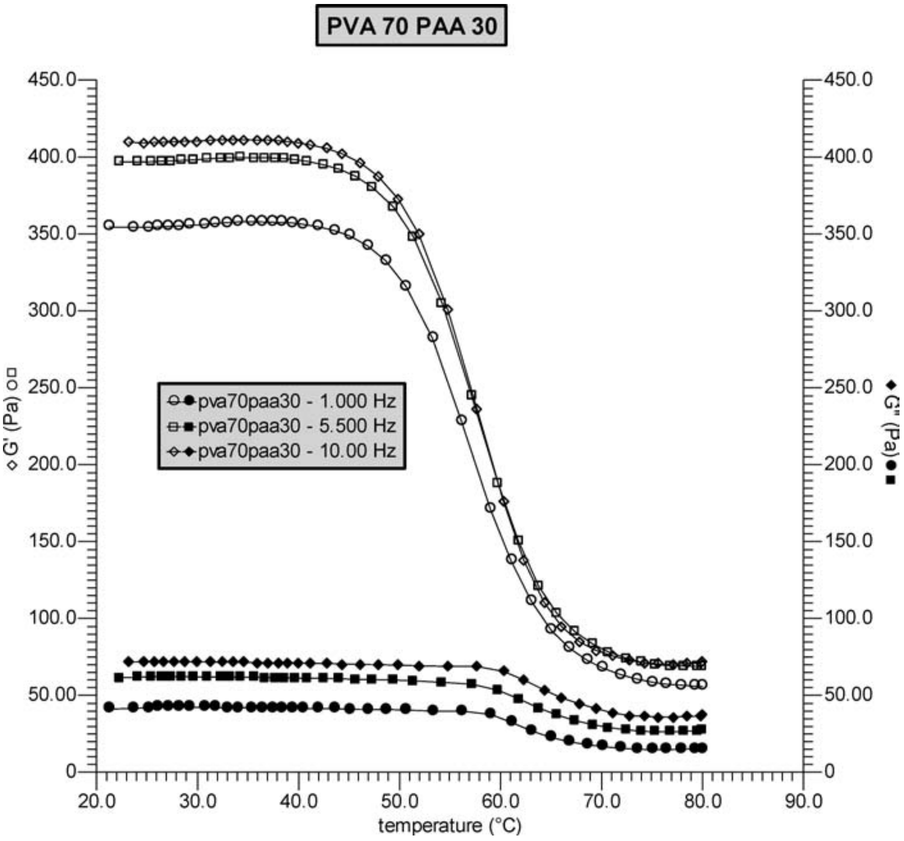

Figure 13 Rheological results for 70 wt% PVA 30 wt% PAA, 10 wt% DMSO hydrogels.

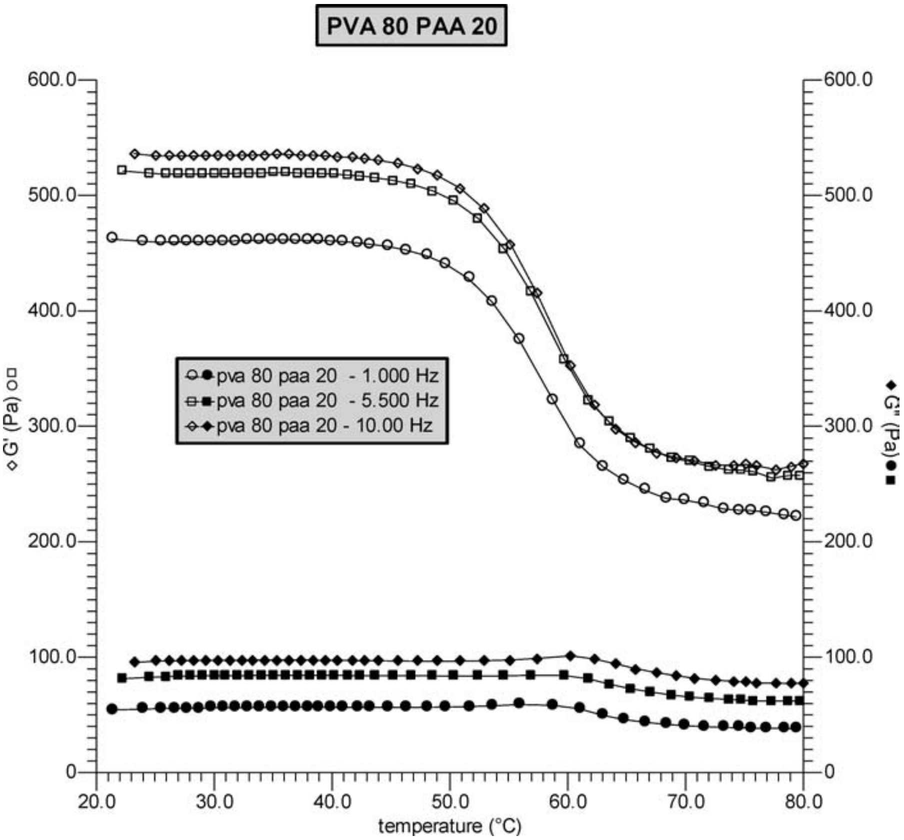

Figure 14 Rheological results for 80 wt% PVA 20 wt% PAA,10 wt% DMSO hydrogels.

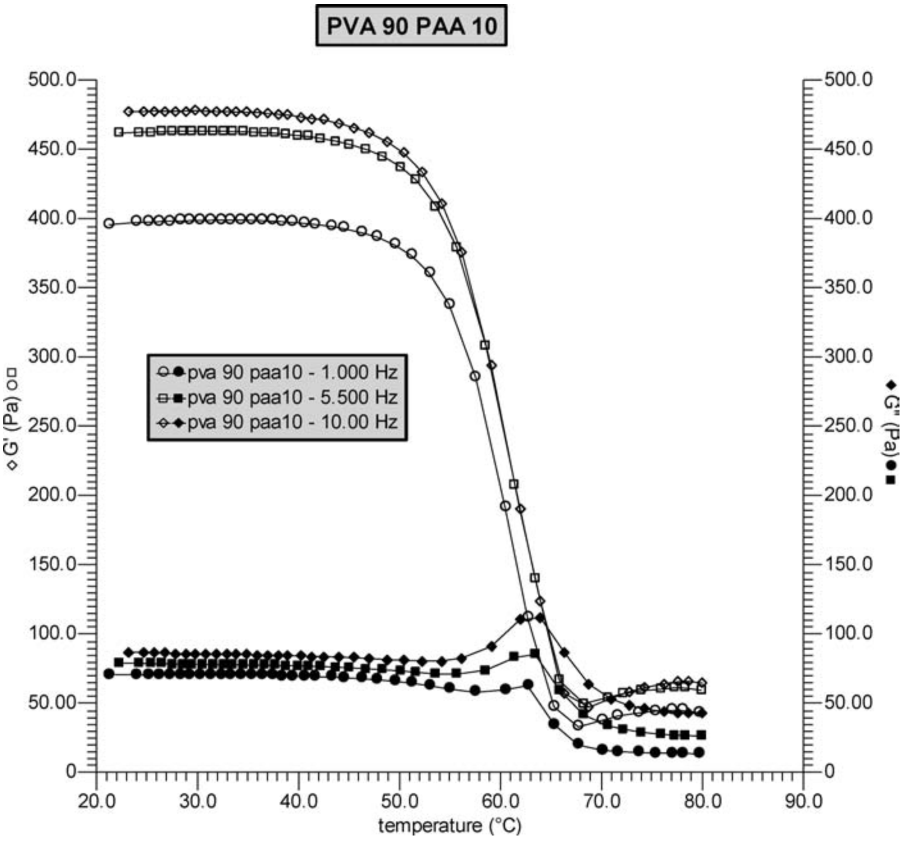

Figure 15 Rheological results for 90 wt% PVA 10 wt% PAA, 10 wt% DMSO hydrogels.

in equations 1 and 2 [42].

$$\text{Strain}\, e = e_0 \sin \omega t \tag{1}$$

$$\text{Strain}\, \sigma = \sigma_0 \sin(\omega t + \delta) \tag{2}$$

where ω is angular frequency and δ is the phase lag. The stress strain relationship can be defined by quantities G' and G'' which are 90° out of phase with the strain [42]. These are described in equations 3 and 4.

$$G' = (\sigma_0/e_0) \cos \delta \tag{3}$$

$$G'' = (\sigma_0/e_0) \sin \delta \tag{4}$$

G' is in phase with the solid and is called the storage modulus because it defines the energy stored in the specimen due to the applied strain and G'' which is $\pi/2$ out of phase with the strain defines the dissipation of energy and is called the loss modulus [42]. It should be noted that for small strain amplitudes G' is independent of the strain amplitude. In the following all the experiments were performed at the low strain amplitude which is the constant regime for G'.

Figs 8 to 11 show the rheological results for 100% aqueous blends of PVA and PAA hydrogels. Figs 12 to 15 shows the rheological results for 10 wt% DMSO blends of PVA and PAA.

PVA gels containing solvents such as a DMSO/water mixture have very complicated and strong physical interactions between solvent and polymer. The rheological properties of the PVA solutions are affected by effectiveness of the physical bonding between the polymer and the solvent [40].

The general trend that emerges, from the results, is that G' is much larger than G'', at 20 to 40°C. This suggests that the elastic response dominates, which is typical for gels and solid-like materials. The values typical of a soft, swollen polymer network are between 500–1000 Pa [43]. The results obtained are close to this range for the 10 wt% DMSO and the 100% aqueous gels, at lower temperatures i.e. 20 to 40°C. The frequency of the test is in the range from 1 Hz to 10 Hz. The higher frequencies results in a negligible increase in G'.

The major differences arise with the use of a different solvent and the findings show that 10 wt% DMSO gels have a dynamic modulus of twice that of aqueous gels in the range of 20 to 40°C. The higher modulus is attributed to the stronger hydrogen bonding between the polymers and the solvent for the 10 wt% DMSO hydrogels. The results indicate that the addition of various amounts of the PAA does not affect the dynamic modulus considerably. This would indicate that the strength of the hydrogels is determined by the presence of the PVA.

The hydrogels are viscoelastic solids with both the storage modulus (G') and loss modulus (G'') being temperature dependent. A significant drop in G' at a temperature in the region of 40°C is observed for both types of gels. The 10 wt% DMSO and the 100% aqueous gels show different responses to the temperature ramp.

For 10 wt% DMSO gels above 40°C, increasing the temperature results in a significant decrease in the storage modulus G'. The value of G' decreases because the material becomes softer. This is expected because the hydration state of DMSO/ water system is so weak that it releases water molecules [40]. Free water forms hydrogel structure and the release of water changes the mechanical properties.

For the 100% aqueous gels a more complicated behavior is observed at temperatures above 40°C. G' first decreases and then increases. PVA solution systems may have some 3-dimensional order at the molecular level due to polar interactions and under shear, some local orientation of the polymer molecules is attained whose degree is dependent on temperature. These oriented regions makes physical bonding through hydroxyl groups stronger. Consequently some oriented gel structure would be developed above a certain temperature and G' increases [40].

4. Conclusion

This paper has described the mechanical and thermal properties of physically cross linked poly (vinyl alcohol)/poly (acrylic acid) hydrogels. The physical and mechanical properties are determined by entanglement, hydrogen bonding, primary and secondary crystallization and phase separation. The hydrogels prepared using a DMSO/water mixture were significantly stronger than those that contained water alone, especially at temperatures of 20 to 40°C. The thermal analysis shows distinct endotherms and evidence of secondary crystallization. The interesting features of the research is that gels with different properties are created by varying the polymer feed ratios and by changing the solvent. The rheometry results showed that the strength of the gels was temperature dependent. This information is useful for thermo responsive systems.

Though the gels created using DMSO were stronger, there is an inherent disadvantage in using DMSO in medical applications. DMSO has to be extracted from the DMSO/water gels for medical applications, because of its toxicity. DMSO is an indispensable component for the DMSO/water gels to keep the elastic modulus at a high level.

Further work is being undertaken to examine the processing parameters for the creation of more functional hydrogels. In addition the work has indicated that the thermal transitions that are present are in the region of interest to drug delivery systems and may be modified by careful blending.

Acknowledgments

This study was supported in parts by grants from both Enterprise Ireland and the Athlone Institute Institute of Technology research and development fund.

References

1. A. S. HOFFMAN, *J. Adv. Drug Delivery Rev.* **43** (2002) 3.
2. B. JONG and A. GUTOWSKA, *Trends Biotechnol.* **20** (2002) 305.
3. A. B. SCRANTON, B. RANGARAJAN and J. KLIER, *Bi. J. Adv. Polym. Sci.* **122** (1995) 1.
4. C. L. BELL and N. A. PEPPAS, *Bi. J. Adv. Polym. Sci.* **122** (1995) 126.
5. S. SERSHEN and J. WEST, *Adv. Drug Delivery Rev.* **54** (2002) 1225.
6. K. D. MAHAVEER and T. M. AMINABHAVI, *P. J. Controlled Release* **96** (2004) 9.
7. T. G. PARK, *Te. Biomaterials* **20** (1999) 517.
8. J. F. YAUNG and T. K. KWEI, *J. applied Polym. Sci.* **69** (1998) 921.
9. A. KISHIDA and Y. IKADA in: "Hydrogels for Biomedical and Pharmaceutical Applications," edited by S. Dumitriu, 2nd ed. (Polymeric Biomaterials, 2002) p. 133.
10. N. A. PEPPAS, P. BURES, W. LEOBANDUNG and H. ICHIKAWA, *J. Pharm. Biopharm.* **50** (2000) 27.
11. S. R STAUFFER and N. A. PEPPAS, *P. J. Poly.* **33** (1992) 3932.
12. P. J. WILLCOX, D. W. HOWIE and K. SCHMIDT ROHR, *J. Poly. Sci.* **37** (1999) 3438.
13. C. M. HASSAN and N. A. PEPPAS, *J. Adv. Poly. Sci.* **153** (2000) 37.
14. OKA MASANORI, TAKASHI NOGUCHI, PRAVEEN KUMAR, KEN IKEUCHI, TAKAO YAMAMURO, S. H. HYON and YOSHITO IKADA, Development of an artificial articular cartilage Clinical Materials **6** (1990) 361.
15. YOUNG MOO LEE, SU HWI KIM and CHONG SOO CHO, *J. Applied Poly. Sci.* **62** (1996) 301.
16. C. M. HASSAN, J. E. STEWART and N. A. E.PEPPAS, *Euro. J. Pharm. Biophar.* **49** (2000) 161.
17. T. SHIGA, H. YOSHIHARU, A. OKADA and K. TOSHIO *J. Applied Poly. Sci.* **44** (1992) 249.
18. J. RUIZ, A. MANTECON and V. CADIZ, *J. Applied Poly. Sci.* **81** (2001) 1444.
19. S. Y. KIM, S. S HEUNG, M. L. YOUNG and C. N. JEONG, *J. Applied Poly. Sci.* **73** (1999) 1656.
20. M. WATASE and K. NISHINAR, *J. Poly. Sci.* **23** (1985) 1803.
21. *Idem.*, *Poly. J.* **21** (1989) 567.
22. T. TANIGAMI, K. MURASE, K. YAMAURA and J. MATSUZAWA, *Poly.* **35** (1994) 2573.
23. N. TAKAHASHI, T. KANAYA, K. NISHIDA and K. KAJI, *Poly.* **44** (2003) 4075.
24. T. KANAYA, H. TAKESHITA, M. NISHIKOJI, M. OHKURA, K. NISHIDA and K. KAJI, *Supramol. Sci.* **5** (1998) 215.
25. M. OHKURA, T. KANAYA and K. KAJI, *Poly.* **33** (1992) 3686.
26. K. NIJENHUIS, *J. Adv. Poly. Sci.* **130** (1997) 3.
27. T. K. L. MEYVIS, B. G. STUBBE, M. J. VAN STEENBERGEN, W. E. HENNINK, S. C. DE SMEDT and J. DEMEESTER, *International J. Pharm.* **244** (2002) 163.
28. T. K. L. MEYVIS, S. C. DE SMEDT and J. DEMEESTER *J. Rheol.* **43** (1999) 933.
29. A. D. WOODSON, R. K. MALCOLM, K. CAMPBELL, D. S. JONES and J. A. RUSSELL, *J. Contr. Rel.* **67** (2000) 395.
30. G. P. ANDREWS, S. P. GORMAN and D. S. JONES, *Biomater.* **26** (2004) 571.
31. D. S. JONES, *International J. Pharm.* **179** (1999) 167.
32. DEVINE D. M. and C. L. HIGGINBOTHAM, *Poly.* **44** (2003) 7851.
33. R. RICCIARDI, C. GAILLET, G. DUCOURET, F. LAFUMA and F. LAUPRETRE, *J. Poly.* **44** (2003) 3375.
34. M. KOBAYASHI, I. ANDO, T. ISHII and S. AMIYA, *J. Molecul. Struc.* **440** (1998) 155.
35. Y. MACHIDA, S. KUROKI, M. KANEKIYO, M. KOBAYASHI, I. ANDO and S. AMIYA, *J. Molecul. Struc.* **554** (2000) 81.
36. E. VERDONCK, K. SCHAAP and L. C. THOMAS, *International J. Pharm.* **192** (1999) 3.
37. J. S. PARK, J. W. PARK and E. RUCKENSTEIN, *Poly.* **42** (2001) 4271.
38. P. MOLYNEUX, *Prop. Ert. Behav.* **1** (1983) 77.
39. T. TANIGAMI, K. MURASE, K. YAMAURA and J. MATSUZAWA, *Poly.* **35** (1994) 2573.
40. L. S. SONG and C. K. BYOUNG, *Poly.* **45** (2004) 2381.
41. N. A. PEPPAS and S. L. WRIGHT, *Europe. J. Pharm. Biopharm.* **46** (1998) 15.
42. I. M. WARD and D. W. HADLEY, "An Introduction to the Mechanical Properties of Solid Polymers" (1993).
43. H. JIANG, W. SU, P.T. MATHER and T.J. BUNNING, *Rheol. Highl. Swollen Chitosan/Polyacryl. Hydrogel. Poly.* **40** (1999) 4593.

Received 12 November 2004
and accepted 29 June 2005